Remarks

I. Support for Amendments

The foregoing amendments to the claims are believed to place the pending claims into condition for allowance. Most of these amendments were discussed by the undersigned with Examiners Pak and Achutamurthy during a personal interview held on August 21, 2002. The amendments to claims 5, 9, 12, 14 and 16 delete subject matter from these claims, and thus add no new matter. The amendments to claim 17 are sought to correct a minor error in the preamble of this claim, and to delete a redundant recitation that is imported into this claim by its dependence from claim 1, and thus add no new matter. The amendment to claim 19 is sought to correct a minor error in the preamble of this claim, and thus adds no new matter. Support for the remaining amendments can be found throughout the specification as originally filed, either inherently or explicitly. Specifically, support for the amendments to claim 33 can be found throughout the specification and in claims 29 and 33 as originally filed; and support for new claims 34-36 can be found in the specification at page 7, lines 12-14. New claim 37 is sought to be entered at the suggestion of the Examiners during the interview, as discussed below, and represents dependent claim 10 written in independent form; support for new claim 37 can be found in the specification at page 4, lines 5-7, and in claim 10 as originally filed.

Hence, no new issues are raised, and no new matter is added, as a result of the foregoing amendments. Therefore, Applicants respectfully request entry and consideration of the foregoing amendments, and reconsideration and withdrawal of the outstanding objections and rejections.

II. Status of the Claims

By the foregoing amendments, claims 10 and 29-32 are cancelled, new claims 34-37 are sought to be entered, and claims 5, 9, 12, 14, 16, 17, 19 and 33 are sought to be amended. These amendments do not add new matter. Upon entry of the foregoing amendments, claims 1-9, 11-28 and 33-37 are pending in the application, with claims 1, 33 and 37 being the independent claims.

Applicants note that the Examiner has indicated on the Office Action Summary (Form PTO-326) attached to Paper No. 14 that claims 11-16 are withdrawn from consideration. It is also noted, however, that in the restriction requirement issued in Paper No. 6 (at page 2), claims 11-16 were included in restriction group I (which comprised claims 1-28 and 33), which was elected without traverse via telephone (*see* Paper No. 6 at page 4, lines 1-3) and in writing (*see* Amendment and Response filed October 4, 2001, at page 2). It is further noted that claims 11-16 were considered by the Examiner as being drawn to a non-elected *species*, the species of mammalian uricase having been elected both via telephone (*see* Paper No. 6 at page 4, line 3) and in writing (*see* Amendment and Response filed October 4, 2001, at page 2). Thus, claims 11-16 were not part of a non-elected restriction group under 37 C.F.R. § 1.142, but instead represent non-elected species under 37 C.F.R. § 1.146. Applicants respectfully assert that generic claim 1 and dependent claim 2 (encompassing the elected species, mammalian uricase) are allowable, in view of the amendments and remarks contained herein. Hence, it is respectfully requested that claims 11-16 be rejoined and examined with the

remaining claims in restriction group I, and that these claims be allowed. *See* 37 C.F.R. § 1.141(a) and 1.146, and MPEP § 809.02(c)(B).

III. Summary of the Interview

Applicants wish to thank Examiners Pak and Achutamurthy for the time taken to discuss the outstanding rejections with Applicants' undersigned representative during a personal interview held on August 21, 2002. During this interview, the merits of the objection and rejections in the outstanding Office Action were discussed, and the Examiners agreed to reconsider the outstanding objection and rejections upon filing of the present Amendment and Reply Under 37 C.F.R. § 1.116.

IV. Summary of the Office Action

In the Office Action dated May 22, 2002 (Paper No. 14), the Examiner has made one objection to, and five rejections of, the claims. Applicants respectfully offer the following remarks to overcome or traverse each element of this rejection in the Office Action.

V. The Objection to Claim 10

In the Office Action at pages 2-3, the Examiner has objected to claim 10 under 37 C.F.R. § 1.75(c) as allegedly being of improper form for failing to further limit the subject matter of claims 1 and 4, from which it ultimately depends. Applicants respectfully traverse this objection, and disagree with the Examiner's assertions made at page 3 in support thereof.

However, to expedite prosecution and allowance of the present application, and not in acquiescence to this objection, claim 10 has been cancelled and rewritten in independent form as new claim 37, as suggested by the Examiner in the Office Action at page 2, final three lines, and as suggested by the Examiners during the interview. Accordingly, this objection has been fully accommodated; reconsideration and withdrawal of the objection under 37 C.F.R. § 1.75(c) are respectfully requested.

VI. The Rejection Under 35 U.S.C. § 112, Second Paragraph, Is Traversed

In the Office Action at pages 3-4, the Examiner has rejected claims 5, 9 and 10 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Applicants respectfully traverse this rejection, in view of the following remarks.

A. The Recitation of "Substantially the Sequence Of"

In making this rejection, the Examiner first contends that claims 5 and 9 are indefinite reciting "substantially the sequence of." Applicants respectfully disagree, and assert that one of ordinary skill could readily determine the metes and bounds of a uricase that has substantially the sequence of a given reference uricase. However, to expedite prosecution and allowance of the present application, and not in acquiescence to this rejection, claims 5 and 9 have been amended to delete the word "substantially." Hence, this portion of the rejection has been accommodated; reconsideration and withdrawal are respectfully requested.

B. The Rejection of Claim 10

The Examiner next contends that claim 10 is indefinite for reciting "...comprises an amino terminal and a carboxy terminus." Paper No. 14 at pages 3-4. By the foregoing amendments, claim 10 has been cancelled. Thus, this portion of the rejection has been rendered moot.

C. Summary

In view of the foregoing remarks, Applicants respectfully assert that the claims as currently presented particularly point out and distinctly claim the subject matter regarded by Applicants as the invention. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, are therefore respectfully requested.

VII. The Rejection Under 35 U.S.C. § 102(b) Over R&D Focus Drug News Is Traversed

In the Office Action at pages 4-5, the Examiner has maintained the rejection of claims 1-8, 17-28 and 33 under 35 U.S.C. § 102(b) as being anticipated by R&D Focus Drug News (Doc. No. V1 on the Form PTO-892 attached to Paper No. 11). Applicants respectfully traverse this rejection.

In making this rejection, the Examiner contends that R&D Focus Drug News discloses each limitation of the presently claimed invention. Applicants respectfully disagree.

Under 35 U.S.C. § 102, a claim can only be anticipated if every element in the claim is expressly or inherently disclosed in a single prior art reference. *See Kalman v. Kimberly*

Clark Corp., 713 F.2d 760, 771 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984). In addition, a claim can only be anticipated by a publication if the publication describes the claimed invention with sufficient enabling detail to place the public in possession of the invention. *See In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985); *see also PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558, 1566 (Fed. Cir. 1996) ("To anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter.").

As one of ordinary skill would readily recognize, the R&D Focus Drug News reference is limited to a one-paragraph announcement of the establishment of a license agreement between BioTechnology General ("BTG"), a source of uricase used in the present invention, and Mountain View Pharmaceuticals (the assignee of the present application) and Duke University. This reference contains no explicit disclosure of purified uricase that is substantially free of aggregates larger than octamers. Moreover, this reference contains no disclosure that would enable one of ordinary skill to make and use the purified uricase preparations of the claimed invention. Thus, R&D Focus Drug News does not expressly anticipate the claimed invention.

Perhaps recognizing these deficiencies of R&D Focus Drug News, the Examiner instead appears to contend that this reference *inherently* discloses the invention. Specifically, the Examiner contends that "[b]ecause the referenced uricase is used as a therapeutic composition in humans, one skilled in the art would recognize that said uricase is free of large

aggregates." Paper No. 14 at page 4, lines 18-19. Applicants respectfully disagree with these contentions.

As discussed in detail above, there is absolutely no evidence that the BTG uricase preparations alluded to in R&D Focus Drug News are substantially free of aggregates larger than octamers. In fact, the opposite is true: the present specification clearly indicates that the uricase preparations obtained from BTG contain high levels of aggregates larger than octamers. Example 1 details the chromatographic purification of uricase, starting with unfractionated uricase obtained from BTG, into high-salt and low-salt fractions. *See* Specification at page 15, and in Figures 1-3. Example 2 discusses the fractionation of the unfractionated BTG uricase by size, clearly indicating that the BTG uricase contains substantial amounts of uricase aggregates larger than octamers. *See* Specification at page 16 and Figures 2-4. Examples 3 and 5 specifically characterize the starting uricase obtained from BTG as "unfractionated" (*see* Specification at page 16, line 21, and at page 18, line 15), which is said to have "the highest content of very large aggregates" (*see* Specification at page 18, lines 15-16, and Figure 2). Finally, Examples 5 and 6 demonstrate that mice injected with unfractionated uricase obtained from BTG develop antibodies that result in the rapid clearance of PEG-uricase conjugates prepared using the unfractionated uricase. *See* Specification at pages 17-19, and Figures 5-6. As is amply discussed in the present specification, uricase aggregates larger than the octameric form are substantially immunogenic (*see*, *e.g.*, Specification at page 3, lines 8-27). Thus, as one of ordinary skill in the art would readily recognize from the disclosure of the present specification, the unfractionated BTG uricase

contains substantial aggregates that are larger than the octameric form, as demonstrated both chromatographically and immunologically.

Moreover, it is simply not true that just because a given uricase preparation is used therapeutically, it is free of large aggregates *a priori* as suggested by the Examiner. In fact, the art demonstrates just the opposite -- that certain preparations of uricase that have been used therapeutically actually induce strong immunogenic (in certain cases, even anaphylactic) responses in humans. *See, e.g.*, Pui *et al.*, *Leukemia 11*:1813-1816 (1997), and Donadio *et al.*, *Nouv. Presse Med. 10*:711-712 (1981) (both of record in Applicants' Information Disclosure Statement filed January 25, 2001); *see also* Leaustic *et al.*, *Rev. Rhum. Mal. Osteoartic. 50*:553-554 (1983); all of which were cited in the present specification at page 2, lines 4-9.

Thus, the Examiner has not offered any objective evidence to support the general contention that uricase preparations used as therapeutic compositions are *a priori* free of large aggregates, and the present specification and the art clearly demonstrate that such preparations in fact are *not* free of large aggregates. Hence, the contention that the unfractionated BTG uricase is free of large aggregates is in error.

The Examiner is reminded that "[i]n order for a disclosure to be inherent . . . the missing descriptive matter must necessarily be present in the [cited reference] such that one skilled in the art would recognize such a disclosure." *Tronzo v. Biomet, Inc.*, 156 F.3d 1154, 1159 (Fed. Cir. 1998). Moreover, to rely on an inherency argument, "the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic *necessarily* flows from the teachings of the applied prior

art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (PTO Bd. Pat. App. Int. 1990) (emphasis in original). That is, inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1269 (Fed. Cir. 1991). In the present case, the Examiner has pointed to no disclosure in R&D Focus Drug News that is "necessarily present" such that it would be recognized as by one of ordinary skill as disclosing uricases that are substantially free of aggregates larger than octamers (thus, the *Tronzo* standard is not met by R&D Focus Drug News). As discussed above, there is no reason to assume that just because a given uricase is used therapeutically it is necessarily substantially free of aggregates larger than octamers. Thus, the Examiner has pointed to no disclosure in R&D Focus Drug News, and has provided no sound scientific reasoning, to support the notion that the missing disclosure in R&D Focus Drug News "*necessarily* flows" from what *is* disclosed in this reference (thus, the *Levy* standard is not met by R&D Focus Drug News). Finally, one of ordinary skill reading R&D Focus Drug News could find no disclosure indicating that it was even possible, let alone probable, that uricase preparations could be obtained from BTG that were substantially free of aggregates larger than octamers (thus, the *Continental Can* standard is not met by R&D Focus Drug News). Hence, the Examiner's attempted reliance upon inherent anticipation in the present case is factually and legally unfounded.

In view of the foregoing remarks, Applicants respectfully assert that R&D Focus Drug News does not expressly or inherently disclose every element of the invention as claimed.

Hence, reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) over R&D Focus Drug News are respectfully requested.

VIII. The Rejection Under 35 U.S.C. § 102(b) Over PURICASE® Is Traversed

In the Office Action at pages 4-5, the Examiner has maintained the rejection of claims 1-8, 17-28 and 33 under 35 U.S.C. § 102(b) as being anticipated by PURICASE®, Registration No. 2,246,623 (Doc. No. U1 on the Form PTO-892 attached to Paper No. 11; hereinafter "PURICASE®"). Applicants respectfully traverse this rejection.

As one of ordinary skill would readily recognize, the PURICASE® reference is limited to a record from the U.S. Trademark Electronic Search System of the existence of a registration for the word mark PURICASE®, which is used to identify pharmaceutical preparations containing uricase coupled to PEG for therapeutic uses. This reference contains no explicit disclosure of purified uricase that is substantially free of aggregates larger than octamers. Moreover, this reference contains no disclosure that would enable one of ordinary skill to make and use the purified uricase preparations of the claimed invention. Thus, PURICASE® does not expressly anticipate the claimed invention.

The Examiner also contends that PURICASE® anticipates the claimed invention because this mark "was first used in commerce from December 17, 1998," which is more than one year prior to the filing date of the present application. *See* Paper No. 14 at page 5, third paragraph, lines 2-3. Applicants respectfully note, however, that this "use in commerce" was not a commercial sale or offer for sale of the goods identified by the PURICASE® mark.

Instead, as is detailed in the accompanying Declaration Under 37 C.F.R. § 1.132 by Merry R. Sherman, Ph.D. (hereinafter "The Sherman Declaration"), this "use in commerce" was limited to an interstate shipment of PEG-uricase conjugates to a contract testing laboratory, under confidentiality, for purposes of pharmacokinetic testing of the conjugates as part of the development of the conjugates. *See* Sherman Declaration at ¶8. This "use in commerce" did not represent a sale of the claimed uricase preparations; in fact, the assignee of the present application, Mountain View Pharmaceuticals, Inc., paid the testing laboratory to have the pharmacokinetic testing performed. *See id.* Hence, this "first use in commerce" that occurred on December 17, 1998, did not place the claimed uricases on sale or otherwise in public use and was not a commercial offer for sale. *See* Sherman Declaration at ¶9. Therefore, the "first use in commerce" listed in the PURICASE® reference does not represent a novelty-barring event under 35 U.S.C. § 102(b). *See Pfaff v. Wells Electronics Inc.*, 525U.S. 55, 67-68, 119 S.Ct. 304, 311-312, 48 USPQ2d 1641, 1646-1647 (1998) (establishing that for a commercial use bar under 35 U.S.C. § 102(b) to apply, the claimed invention must be the subject of a commercial offer for sale).

Again, perhaps recognizing these deficiencies of PURICASE® as an expressly anticipatory reference, the Examiner appears to rely again upon inherency. Specifically, the Examiner again contends that since the uricase discussed in the PURICASE® reference is to be used therapeutically, "one skilled in the art would recognize that said uricase is free of large aggregates." Paper No. 14 at page 5, third paragraph, lines 3-5. Applicants respectfully disagree with this contention, for the reasons detailed above and which are reiterated and

incorporated herein by reference. The Examiner has not offered any objective evidence to support the general contention that uricase preparations used as therapeutic compositions are *a priori* free of large aggregates, and the present specification and the art clearly demonstrate that such preparations in fact are *not* free of large aggregates. Hence, it is incorrect to contend that the uricases used in PURICASE® brand uricase conjugates and compositions are necessarily free of large aggregates simply because they are intended to be used therapeutically. Thus, the Examiner's attempted reliance upon inherent anticipation in the present case is factually and legally unfounded.

Hence, PURICASE® does not expressly or inherently disclose the preparation of uricase that is substantially free of aggregates larger than octamers. Moreover, in view of the information contained in the Sherman Declaration, the goods identified by the PURICASE® trademark were not on sale or in public use, or the subject of a commercial offer for sale, more than one year prior to the filing of the present application. Hence, this reference cannot and does not anticipate the present invention. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) over Puricase® are respectfully requested.

IX. The First Rejection Under 35 U.S.C. § 103(a) Is Traversed

In the Office Action at pages 5-6, the Examiner has maintained the rejection of claims 1, 4 and 9 under 35 U.S.C. § 103(a) as being obvious over PURICASE® in view of Wu *et al.*, *Proc. Natl. Acad. Sci. USA 86*:9412-9416 (1989) (of record in Applicants' Information

Disclosure Statement filed January 25, 2001; hereinafter "Wu"). Applicants respectfully traverse this rejection.

In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See In re Piasecki*, 223 USPQ 785, 787-88 (Fed. Cir. 1984). The Examiner can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references in such a way as to produce the invention as claimed. *See In re Fine*, 5 USPQ2d 1596,1598 (Fed. Cir. 1988). Specifically, there must be a reason, suggestion, or motivation in the cited art that would motivate one of ordinary skill to combine the references, and that would also suggest a reasonable likelihood of success in making or using the invention as claimed as a result of that combination. *See In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). In the present case, a *prima facie* case of obviousness has not been established.

Applicants reiterate and incorporate herein the remarks made above concerning the disclosure of PURICASE®. This reference does not disclose, suggest, or otherwise contemplate the production of purified uricase that is substantially free of aggregates larger than octamers. Thus, PURICASE® is seriously deficient as a primary reference upon which to base a *prima facie* case of obviousness.

These deficiencies of the PURICASE® reference are not cured by Wu, which also contains no disclosure, suggestion or contemplation of the production of purified uricase that is substantially free of aggregates larger than octamers. In fact, the alleged motivation relied

upon by the Examiner to justify the combination of the disclosures of PURICASE® and Wu is based on an error. Specifically, the Examiner contends that it is well known in the art that uricase is a copper-binding protein, referring to statements in Wu to this effect. *See* Paper No. 14 at page 5, final paragraph. While it is true that early researchers who studied impure preparations of uricase (*e.g.* Mahler *et al.*, *J. Biol. Chem.* 216:625-641 (1955), cited as Doc. No. AS11 in the Third Supplemental Information Disclosure Statement ("IDS") filed herewith) reported that uricase contained copper, later workers who studied more highly purified preparations of uricase (*e.g.* Conley and Priest, *Biochem. J. 187*: 727-732 (1980), cited as Doc. No. AR11 in the IDS filed herewith) reported that uricase did not contain copper. Moreover, it subsequently has been confirmed conclusively by high-resolution X-ray crystallography that uricase is *not* a copper-binding protein. *See* Colloc'h *et al.*, *Nature Struct. Biol. 4*:947-952 (1997), cited as Doc. No. AT10 in the IDS filed herewith (demonstrating that the active site of urate oxidase catalyzes the oxidation of uric acid without the involvement of "any ions or prosthetic groups" (Colloc'h, abstract), and that "no significant residual peak [in the electron density map of uricase] could correspond to a metal ion" (*id.*, page 951, col.1, final paragraph)). One of ordinary skill therefore would have concluded from the report of Conley and Priest (1980) and the sensitive crystallographic studies reported in Colloc'h (1997) that uricase is not a copper-binding protein, and thus, that the statements to the contrary in Wu (which are based on less sensitive and less specific studies than those in Conley and Priest and in Colloc'h) are in error. Hence, there would have been no motivation

to combine the disclosures of Puricase® and Wu in the attempt to make and use the claimed uricase preparations.

Thus, neither PURICASE® nor Wu suggests that one of ordinary skill should combine the disclosures of PURICASE® and Wu in order to make and use the claimed invention, and one of ordinary skill would not otherwise have been motivated to combine their disclosures. Absent such suggestion and motivation, the cited references may not be properly combined to render the claimed invention obvious. *See In re Fine*, 5 USPQ2d 1596,1598 (Fed. Cir. 1988). Accordingly, the burden required to sustain a *prima facie* case of obviousness has not been met.

In view of the foregoing remarks, Applicants respectfully assert that claims 1, 4 and 9 are not rendered obvious by PURICASE® and Wu, alone or in combination. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) are therefore respectfully requested.

X. The Second Rejection Under 35 U.S.C. § 103(a) Is Traversed

In the Office Action at pages 5-6, the Examiner has maintained the rejection of claims 1, 4 and 10 under 35 U.S.C. § 103(a) as being obvious over PURICASE® in view of Wu. By the foregoing amendments, claim 10 has been cancelled, rendering moot the portion of this rejection that may have applied to this claim. Applicants respectfully traverse this rejection as it may be applied to claims 1 and 4, and to new claim 37, which is sought to be entered in place of cancelled claim 10.

Applicants reiterate and incorporate herein the remarks made above concerning the disclosure of PURICASE®. This reference does not disclose, suggest, or otherwise contemplate the production of purified uricase that is substantially free of aggregates larger than octamers. Thus, PURICASE® is seriously deficient as a primary reference upon which to base a *prima facie* case of obviousness.

These deficiencies in PURICASE® are not cured by the disclosure of Wu, which also contains no disclosure, suggestion or contemplation of the production of purified uricase that is substantially free of aggregates larger than octamers. The alleged motivation to combine Wu with PURICASE® relied upon by the Examiner (*see* Paper No. 14 at page 6, lines 16-18) is irrelevant, since the importance of residues at the N-terminus of uricase on enzymatic activity has no bearing on whether or not purified uricases (or even fragments thereof) that are substantially free of aggregates larger than octamers can be made and used. Hence, there would have been no motivation to combine the disclosures of PURICASE® and Wu in the attempt to make and use the claimed uricase preparations. Since neither the suggestion nor requisite motivation to combine their disclosures is found in PURICASE® and Wu, these references may not be properly combined to render the claimed invention obvious. *See In re Fine*, 5 USPQ2d 1596,1598 (Fed. Cir. 1988). Accordingly, the burden required to sustain a *prima facie* case of obviousness has not been met.

In view of the foregoing remarks, Applicants respectfully assert that claims 1 and 4 (and new claim 37, which replaces cancelled claim 10) are not rendered obvious by

PURICASE® and Wu, alone or in combination. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) are therefore respectfully requested.

XI. Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider and withdraw all of the outstanding objections and rejections.

It is believed that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt entry and favorable consideration of the foregoing amendments and remarks, and allowance of all pending claims, are earnestly solicited.

Respectfully submitted,

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Version with markings to show changes made

In the Claims:

(a) Claims 10 and 29-32 are cancelled without prejudice or disclaimer.

(b) New claims 34-37 are sought to be entered.

(c) Claims 5, 9, 12, 14, 16, 17, 19 and 33 are sought to be amended as follows:

5. (Once amended) The uricase of Claim 4, wherein the uricase has [substantially] the sequence of porcine, bovine, ovine or baboon liver uricase.

9. (Twice amended) The uricase of Claim 4, wherein the uricase has [substantially] the sequence as set forth in SEQ ID NO:2, wherein tyrosine 97 has been replaced by histidine.

12. (Once amended) The uricase of Claim 11, wherein the fungal or microbial uricase is isolated from *Aspergillus flavus*, *Arthrobacter globiformis*, *Bacillus sp.* or *Candida utilis*, or is a recombinant enzyme having [substantially] the sequence of one of said uricases.

14. (Once amended) The uricase of Claim 13, wherein the invertebrate uricase is isolated from *Drosophila melanogaster* or *Drosophila pseudoobscura*, or is a recombinant enzyme having [substantially] the sequence of one of said uricases.

16. (Once amended) The uricase of Claim 15, wherein the plant uricase is isolated from root nodules of *Glycine max* or is a recombinant enzyme having [substantially] the sequence of said uricase.

17. (Once amended) A uricase conjugate comprising the [The] uricase of Claim 1 conjugated to poly(ethylene glycol) or poly(ethylene oxide). [poly(ethylene oxide), wherein the uricase in said conjugate is substantially free of aggregates larger than octamers.]

19. (Once amended) The uricase conjugate of Claim 17, wherein said uricase is conjugated to said poly(ethylene glycol) or poly(ethylene oxide) via a linkage selected from the group consisting of urethane (carbamate), secondary amine and amide.

33. (Once amended) Isolated uricase prepared by a method comprising separating uricase aggregates larger than octamers from uricase tetramers and octamers, and excluding such aggregates from the isolated uricase. [the method of claim 29.]